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THE NARCOTIC ACTION OF XENON

(Read on 23 November 1946 at the session of the Leningrad Society of Physiologists, Biochemists and Pharmacologists dedicated to the 100th anniversary of surgical anesthesia).

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Data on the narcotic action of the so-called "physiologically inactive" gases, nitrogen, methane and the heavier rare gases, was published by N. V. Lazarev as far back as 1941. It was proven that these gases were only slightly soluble in water and, obviously, the amount of these gases in organic tissues is so small that they can produce narcosis only in a compression chamber at pressures of about ten atmospheres. In the case of helium and also, evidently, hydrogen (see Lazarev, 1943), a pressure of over a hundred atmospheres is required to produce narcosis.

The discovery of the narcotic properties of inert gases belonging to the zero group of the periodic table is of particular interest from the theoretical aspect. In view of the complete chemical inertness of these gases, their narcotic property is a convincing argument in favor of the idea, still held in doubt by some (Oswald 1924; Koehnmann, 1936), that the mechanism of the narcotic effect is unrelated to any purely chemical reaction between the narcotic and the living substrate.

The strength of the narcotic action of the rare gases increases with their atomic (molecular) weight. Although complete narcosis of an adult white mouse was not observed with a helium pressure of almost 100 atmospheres, still under these conditions a slight narcotic action was clearly indicated by various symptoms. Argon however, caused narcosis in an adult mouse at a partial pressure of about 16 - 18 atmospheres; and in a young mouse weighing about 5 gm, at 11 atmospheres. With krypton, narcosis was observed in the same mouse at a partial pressure of  $3\frac{1}{2}$  atmospheres.

- 1 -

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50X1-HUM

This data led Lazarev to a glaring paradox in 1941: "Judging from the increase in solubility, the effect of xenon should be almost twice that of Krypton. And if the true strength of the narcotic action, determined by the narcotic concentration in water, increases in the same manner as from helium to krypton, then xenon should induce narcosis at a partial pressure less than one atmosphere. In other words, it can be assumed that the ordinary air of the atmosphere contains a high narcotic dilution strong enough for use in inducing narcosis even at normal atmospheric pressure."

We succeeded in obtaining a small amount of xenon to determine the accuracy of this hypothesis or, to be precise, a xenon-krypton mixture, containing 88 percent xenon and 12 percent krypton. However, the last war denied us the privilege of carrying out this work for a long time and these scheduled tests were performed after a lapse of several years.

Three tests were carried out on small mice weighing about 5 gm in the small compression chamber previously described (Lazarev, 1941). The pressure was created by the movement of a piston. As in the other experiments with inert gases previously described, the pressure chamber was "washed through" with oxygen before the start of the actual test. This operation served two purposes: (1) the creation of a certain "reserve" of oxygen necessary for respiration of the animal during the test; and (2) it enabled one to consider, when analyzing gas samples from the chamber, that the entire volume remaining in the gas burette after absorption of the oxygen and carbon dioxide was composed of the inert gas used in the test (since nitrogen was almost completely removed from the chamber and even eliminated from the body of the animal when the chamber was "washed through" with oxygen).

We shall take the data of one such test as an example. (In general, all the tests gave similar results.) When "washing through" with oxygen had been completed, the (young) mouse quickly and energetically resumed its normal posture when the chamber was inverted. The time taken to add the xenon was 2 minutes. One minute later, the mouse did not react at all to the inversion of the chamber, being evidently in a state of complete narcosis. Twelve minutes after the introduction of xenon a sample was taken from the chamber. Analysis showed that the gaseous mixture contained 48.5 percent of xenon at a general absolute pressure of one atmosphere. (More accurately, a xenon-krypton mixture of the above composition. This reservation should be borne in mind in all cases where xenon content is given.) After another 2 minutes the animal was removed from the chamber. It was found (as was to be expected, considering the small coefficient of solubility of xenon in water and, consequently, the greater speed of saturation and desaturation of organs with a good blood supply, including the central nervous system) that xenon narcosis not only comes on rapidly but also passes off rapidly. One minute after the mouse had been removed from the atmosphere containing the narcotic it turned over on his stomach and after 3 minutes it was crawling, although unsteadily.

It is of interest to see how xenon affects an adult white mouse. The small amount of gas at our disposal made such tests very difficult. The pressure chamber which we were using for the experiments with young mice was too small for adult mice. After numerous attempts we adopted the following procedure.

The chamber used was a small glass with four branches, ordinarily employed in experiments with isolated sections of smooth-muscle organs (using N. P. Kravkov's method). The bottom of the glass and one branch pipe were flooded with paraffin so as to decrease its volume. On top, the glass was hermetically sealed by means of a rubber stopper which fitted well below the rim. A three-way cock was connected to one of the branches and a disc-shaped rubber balloon to the second. This balloon collapsed readily at the least negative pressure. Its volume was 70 cc and it served as a compensator, maintaining atmospheric pressure in the chamber. The remaining branch was connected to a small 20-cc rubber balloon (pyriform) via a glass tube filled with pieces of caustic soda. The branch to which the compensator was connected was also filled with solid potassium alkali.

- 2 -

CONFIDENTIAL

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50X1-HUM

After the mouse had been placed in the chamber, the gaseous mixture was set in motion and freed of carbon dioxide by alternate compression and deflation of the balloon.

The whole system was "washed through" with oxygen by squeezing the compensator and small balloon (with the three-way cock "to air") and subsequent suction of the oxygen (with the cock turned "to oxygen"). This process was repeated at least ten times. After washing through, all the xenon at our disposal at that time (49 cc) was sucked in.

This test was carried out on a mouse weighing 15 gm under the following conditions. One minute after the xenon had been introduced, a sample taken from the chamber contained 67.4 percent of this gas (carbon dioxide 0 percent). After 5 minutes when the chamber was inverted, we clearly observed that the mouse was resuming its normal posture more and more slowly, using its forelegs only for this purpose. By this time the hindlegs were quite paralyzed. The animal was shuddering all over, and this became more and more violent. Nine minutes after the introduction of the xenon, another sample of the gas mixture was taken: it was found to contain 75 percent xenon and absolutely no carbon dioxide. One minute later, when the chamber was inverted, the animal failed to resume its normal position completely.

It can be seen from this data that xenon also exercises a distinct narcotic action on an adult mouse although there was no complete narcosis, even at a partial pressure of this gas of  $3/4$  atmosphere. Tentatively, it may be considered in this experiment that xenon must have had a partial pressure not greater than one atmosphere.

We did not observe the process of restoration of functions in the adult mouse after it was removed from the narcotic atmosphere. The xenon was displaced from the chamber by water, thereby drowning the mouse, in order to collect the gas in other experiments after removal of oxygen and  $CO_2$ .

It may also be mentioned briefly that we also tested the action of xenon on insects (cockroaches). Due to the fact that only a small amount of xenon was at our disposal, we were able to produce only a partial pressure of 3.1 atmospheres (with a total pressure of 4.4 atmospheres). Under these conditions the cockroaches continued to move but lost their balance easily and rolled to the bottom of the chamber, where they lay for most of the time. At lower partial pressures of xenon (about 2 - 2.5 atmospheres) it was observed that the insects were stimulated and moved about the chamber much more energetically than before the experiment. On the other hand, at a still lower partial pressure of the gas (about 0.7 - 1 - 1.5 atmospheres) the cockroaches indicated a unique torpor. They stood completely motionless in the pose they had assumed. "Like a statue" is the phrase used in our records.

Thus, the prediction we made some years ago, that xenon as normally found in air is a strong narcotic and can exercise its narcotic action even at normal barometric pressure, is fully justified. The narcotic action of xenon is several times stronger than that of krypton.

The experiments published previously (Iazarev, 1941) sometimes evoked a certain skepticism. It was suggested that the paralysis of animals observed, although outwardly similar to narcosis, was in reality due to the purely mechanical effect of high pressure. It is true that even then it was possible to develop a fairly strong case against an objection of this kind:

1. Paralysis of the animals is observed at completely different total pressures when the barocamera is filled with various gaseous mixtures.
2. It is possible, knowing the solubility coefficients of various "physiologically inert" gases in water and therefore, approximately, in blood and tissue fluid, to calculate what should be the content of this or that inert gas in an animal organism while in the chamber at the pressure at which paralysis of the

- 3 -

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animal is observed. The result of calculation is that this content is exactly the same as that at which one would expect the particular substance to produce narcosis, working from the existing data on its physicochemical properties, in particular, the Overton-Meyer coefficient of distribution between olive oil and water. A coincidence of this type, repeated several times, cannot be accidental.

Our experiments with xenon, which have shown that an inert gas can display distinct narcotic properties even at normal barometric pressures, are authentic and conclusive proof that the inert gases act as narcotics independently of changes in atmospheric pressure and that this narcotic action is possible even if the substance is known to be incapable of entering into any chemical reactions whatsoever within the organism.

NOTE: After we had read the paper on the above tests, a report by a group of American researchers (Lawrence and co-authors) on the narcotic action of xenon on white mice made its appearance on 6 December 1946. Their report is in full agreement with our results.

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